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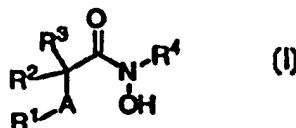
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(21) International Application Number: PCT/US98/02987 (22) International Filing Date: 17 February 1998 (17.02.98) (30) Priority Data: 08/806,728 27 February 1997 (27.02.97) US (71) Applicant: AMERICAN CYANAMID COMPANY [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventors: VENKATESAN, Aranapakam, Mudumbai; 97-07 63rd Road #9K, Rego Park, NY 11374 (US). GROSU, George, Theodore; 117 Prospect Place, Pearl River, NY 10965 (US). DAVIS, Jamie, Marie; 20 High Avenue, Nyack, NY 10960 (US). BAKER, Jannie, Lea; 127 Rockinchair Road, White Plains, NY 10607 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Cor- poration, One Campus Drive, Parsippany, NJ 07054 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

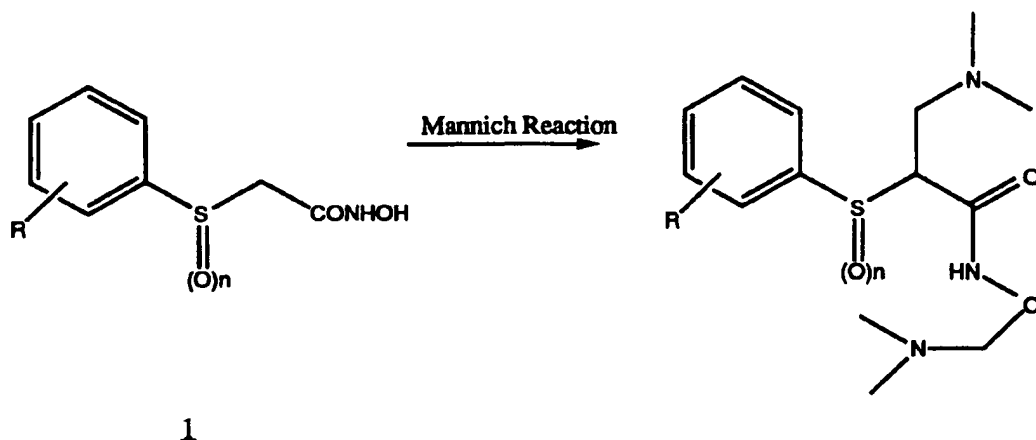
(54) Title: N-HYDROXY-2-(ALKYL, ARYL OR HETEROARYL SULFANYL, SULFINYL OR SULFONYL)-3-SUBSTITUTED ALKYL, ARYL OR HETEROARYLAMIDES AS MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract

Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes. These zinc containing



endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. TNF- $\alpha$  converting enzyme (TACE), a pro-inflammatory cytokine, catalyzes the formation of TNF- $\alpha$  from membrane bound TNF- $\alpha$  precursor protein. It is expected that small molecule inhibitors of MMPs and TACE therefore have the potential for treating a variety of disease states. The present invention provides low molecular weight, non-peptide inhibitors of matrix metalloproteinases (MMPs) and TNF- $\alpha$  converting enzyme (TACE) for the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, diabetes (insulin resistance) and HIV infection having formula (I) wherein R<sup>2</sup> and R<sup>3</sup> form a heterocyclic ring and A is S, S(O), or S(O)<sub>2</sub>, and R<sup>1</sup> and R<sup>4</sup> are defined herein.

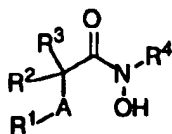


Some sulfone carboxylic acids are disclosed in U.S. patent 4,933,367. Those compounds were shown to exhibit hypoglycemic activity.

#### SUMMARY OF THE INVENTION:

The present invention relates to novel, low molecular weight, non-peptide inhibitors of matrix metalloproteinases (MMPs) and TNF- $\alpha$  converting enzyme (TACE) for the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, diabetes (insulin resistance) and HIV infection.

In accordance with this invention there is provided a group of compounds of general formula I



wherein:

$\text{R}^1$  is alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from  $\text{R}^5$ ;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from  $\text{R}^5$ ;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from  $\text{R}^5$ ;

aryl of 6 to 10 carbon atoms, optionally substituted with one or two groups selected independently from  $R^5$ ;  
cycloalkyl of 3 to 8 carbon atoms, optionally substituted with one or two groups selected independently from  $R^5$ ;  
5 saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or  $NR^7$ , optionally substituted with one or two groups selected independently from  $R^5$ ;  
or heteroaryl- $(CH_2)_{0-6}$ - wherein the heteroaryl group is 5 to 6 membered with one or two heteroatoms selected independently from O, S, and N and may be  
10 optionally substituted with one or two groups selected independently from  $R^5$ ;

A is -S-, -SO- or  $SO_2$ -;

$R^2$  and  $R^3$ , taken with the carbon atom to which they are attached, form a 5 to 7 membered  
15 heterocyclic ring containing O, S or N- $R^7$  optionally having one or two double bonds;

$R^4$  is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from  $R^5$ ;  
20 alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from  $R^5$ ;  
alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from  $R^5$ ;  
phenyl or naphthyl optionally substituted with one or two groups selected  
25 independently from  $R^5$ ;  
 $C_3$  to  $C_8$  cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from  $R^5$ ;  
saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or  $NR^7$ , optionally substituted with one or  
30 two groups selected independently from  $R^5$ ;

$R^5$  is H,  $C_7$ - $C_{11}$  aroyl,  $C_2$ - $C_6$  alkanoyl,  $C_1$  to  $C_{12}$  alkyl,  $C_2$  to  $C_{12}$  alkenyl,  $C_2$ - $C_{12}$  alkynyl, F, Cl, Br, I, CN, CHO,  $C_1$ - $C_6$  alkoxy, aryloxy, heteroaryloxy,  $C_3$ - $C_6$  alkenyloxy,  $C_3$ - $C_6$  alkynyloxy,  $C_1$ - $C_6$  alkoxyaryl,  $C_1$ - $C_6$  alkoxyheteroaryl,  $C_1$ - $C_6$  alkylamino- $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_2$  alkylene dioxy, aryloxy- $C_1$ - $C_6$  alkyl amine,  $C_1$ - $C_{12}$   
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perfluoro alkyl,  $S(O)_n$ -C<sub>1</sub>-C<sub>6</sub> alkyl,  $S(O)_n$ -aryl where n is 0, 1 or 2; OCOO C<sub>1</sub>-C<sub>6</sub> alkyl, OCOOaryl, OCONR<sup>6</sup>, COOH, COO C<sub>1</sub>-C<sub>6</sub> alkyl, COOaryl, CONR<sup>6</sup>R<sup>6</sup>, CONHOH, NR<sup>6</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>6</sup>R<sup>6</sup>, NR<sup>6</sup>SO<sub>2</sub>aryl, -NR<sup>6</sup>CONR<sup>6</sup>R<sup>6</sup>, NHSO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NHheteroaryl, SO<sub>2</sub>NHCOaryl, CONHSO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CONHSO<sub>2</sub>aryl, SO<sub>2</sub>NHCOaryl, CONHSO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CONHSO<sub>2</sub>aryl, NH<sub>2</sub>, OH, aryl, heteroaryl, C<sub>3</sub> to C<sub>8</sub> cycloalkyl; or saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR<sup>7</sup>, wherein C<sub>1</sub>-C<sub>6</sub> alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR<sup>7</sup> and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy;

R<sup>6</sup> is H, C<sub>1</sub> to C<sub>18</sub> alkyl optionally substituted with OH; C<sub>3</sub> to C<sub>6</sub> alkenyl, C<sub>3</sub> to C<sub>6</sub> alkynyl, C<sub>1</sub> to C<sub>6</sub> perfluoro alkyl,  $S(O)_n$ -C<sub>1</sub>-C<sub>6</sub> alkyl  $S(O)_n$  aryl where n is 0, 1 or 2; or COheteroaryl, wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR<sup>7</sup> and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy;

and R<sup>7</sup> is C<sub>7</sub>-C<sub>11</sub> aroyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>12</sub> perfluoro alkyl,  $S(O)_n$ -C<sub>1</sub>-C<sub>6</sub>-alkyl,  $S(O)_n$ -aryl where n is 0, 1 or 2; COO-C<sub>1</sub>-C<sub>6</sub>-alkyl, COOaryl, CONHR<sup>6</sup>, CONR<sup>6</sup>R<sup>6</sup>, CONHOH, SO<sub>2</sub>NR<sup>6</sup>R<sup>6</sup>, SO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NHheteroaryl, SO<sub>2</sub>NHCOaryl, CONHSO-C<sub>1</sub>-C<sub>6</sub>-alkyl, CONHSO<sub>2</sub>aryl, aryl, or heteroaryl, where aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy; and heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or N-C<sub>1</sub>-C<sub>6</sub> alkyl;

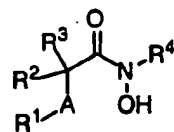
alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

arylalkyl of 7 to 16 carbon atoms, wherein aryl is optionally substituted with one or  
 two groups selected independently from  $R^5$ ;  
 biphenylalkyl of 13 to 18 carbon atoms, wherein biphenyl is optionally substituted with  
 one or two groups selected independently from  $R^5$ ;  
 5 arylalkenyl of 8 to 16 carbon atoms, wherein aryl is optionally substituted with one or  
 two groups selected independently from  $R^5$ ;  
 cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, wherein the cycloalkyl or  
 bicycloalkyl group is optionally substituted with one or two groups selected  
 independently from  $R^5$ ;  
 10 saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom  
 selected from O, S or N- $C_1-C_6$  alkyl, optionally substituted with one or two  
 groups selected independently from  $R^5$ ; or  
 $R^8R^9N-C_1-C_6$ -alkoxyaryl- $C_1-C_6$ -alkyl where  $R^8$  and  $R^9$  are independently selected  
 from  $C_1-C_6$  alkyl or  $R^8$  and  $R^9$  together with the interposed nitrogen forms a  
 15 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom,  
 wherein the aryl group is phenyl or naphthyl;  
 and the pharmaceutically acceptable salts thereof.

A more preferred aspect of the present invention is the group of compounds of general  
 20 formula (Ia):



Ia

25 wherein:

$R^1$  is alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected  
 independently from  $R^5$ ;  
 alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted  
 with one or two groups selected independently from  $R^5$ ;  
 30 alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted  
 with one or two groups selected independently from  $R^5$ ;  
 aryl of 6 to 10 carbon atoms, optionally substituted with one to two groups selected  
 independently from  $R^5$ ;

cycloalkyl of 3 to 8 carbon atoms, optionally substituted with one to two groups selected independently from R<sup>5</sup>;  
 saturated or unsaturated mono or bicyclic heterocycle of from 5 to 10 members containing one heteroatom selected from O, S or NR<sup>7</sup>, optionally substituted with one to two groups selected independently from R<sup>5</sup>;  
 or heteroaryl-(CH<sub>2</sub>)<sub>0-6</sub> wherein the heteroaryl group is 5 to 6 membered with one or two heteroatoms selected independently from O, S, and N and may be optionally substituted with one or two groups selected independently from R<sup>5</sup>;

10 A is -S-, -SO- or SO<sub>2</sub>-;

R<sup>2</sup> and R<sup>3</sup>, taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N-R<sup>7</sup> optionally having one or two double bonds;

15

R<sup>4</sup> is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

20

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R<sup>5</sup>;

25

C<sub>3</sub> to C<sub>8</sub> cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R<sup>5</sup>;

R<sup>5</sup> is H, F, Cl, Br, I, CN, CHO, C<sub>7</sub>-C<sub>11</sub> aroyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub> to C<sub>12</sub> alkyl, C<sub>2</sub> to C<sub>12</sub> alkenyl, C<sub>2</sub>-C<sub>12</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryloxy, heteroaryloxy, C<sub>3</sub>-C<sub>6</sub> alkenyloxy, C<sub>3</sub>-C<sub>6</sub> alkynyloxy, C<sub>1</sub>-C<sub>6</sub> alkoxyaryl, C<sub>1</sub>-C<sub>6</sub> alkoxyheteroaryl, C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>2</sub>-alkylene dioxy, aryloxy-C<sub>1</sub>-C<sub>6</sub> alkyl amine, C<sub>1</sub>-C<sub>12</sub> perfluoro alkyl, S(O)<sub>n</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, S(O)<sub>n</sub>-aryl where n is 0, 1 or 2; OCOO-C<sub>1</sub>-C<sub>6</sub> alkyl, OCOOaryl, OCONR<sup>6</sup>, COOH, COO-C<sub>1</sub>-C<sub>6</sub> alkyl, COOaryl, CONR<sup>6</sup>R<sup>6</sup>, CONHOH, NR<sup>6</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>6</sup>R<sup>6</sup>, NR<sup>6</sup>SO<sub>2</sub>aryl, NR<sup>6</sup>CONR<sup>6</sup>R<sup>6</sup>, NHSO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NHheteroaryl, SO<sub>2</sub>NHCOaryl, CONHSO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CONHSO<sub>2</sub>aryl, SO<sub>2</sub>NHCOaryl,

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CONHSO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CONHSO<sub>2</sub>aryl, NH<sub>2</sub>, OH, aryl, heteroaryl, C<sub>3</sub> to C<sub>8</sub> cycloalkyl; or saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR<sup>7</sup>;

wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR<sup>7</sup> and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy;

R<sup>6</sup> is H, C<sub>1</sub> to C<sub>18</sub> alkyl optionally substituted with OH; C<sub>3</sub> to C<sub>6</sub> alkenyl, C<sub>3</sub> to C<sub>6</sub> alkynyl, C<sub>1</sub> to C<sub>6</sub> perfluoro alkyl, S(O)<sub>n</sub> alkyl or aryl where n is 0, 1, or 2; or COheteroaryl;

wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR<sup>7</sup> and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy;

and R<sup>7</sup> is C<sub>7</sub>-C<sub>11</sub> aroyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>12</sub> perfluoro alkyl, S(O)<sub>n</sub>-alkyl, S(O)<sub>n</sub>-aryl where n is 0, 1 or 2; COOalkyl, COOaryl, CONHR<sup>6</sup>, CONR<sup>6</sup>R<sup>6</sup>,

CONHOH, SO<sub>2</sub>NR<sup>6</sup>R<sup>6</sup>, SO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NHheteroaryl, SO<sub>2</sub>NHCOaryl, CONHSO<sub>2</sub>alkyl, CONHSO<sub>2</sub>aryl, aryl, heteroaryl; wherein C<sub>1</sub>-C<sub>6</sub> alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR<sup>7</sup> and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy; alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

arylalkyl of 7 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R<sup>5</sup>;

biphenylalkyl of 13 to 18 carbon atoms, wherein biphenyl is optionally substituted with one or two groups selected independently from R<sup>5</sup>;



arylalkenyl of 8 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from  $R^5$ ;

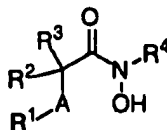
cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, wherein cycloalkyl or bicycloalkyl is optionally substituted with one or two groups selected independently from  $R^5$ ;

saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or N- $C_1-C_6$  alkyl, optionally substituted with one or two groups selected independently from  $R^5$ ;

$R^8R^9N-C_1-C_6$ -alkoxyaryl- $C_1-C_6$ -alkyl where  $R^8$  and  $R^9$  are independently selected from  $C_1-C_6$  alkyl or  $R^8$  and  $R^9$  together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

The most preferred group of compounds are those of the following formula (Ib):



Ib

in which

$R^1$  is phenyl, naphthyl, alkyl of 1-18 carbon atoms or heteroaryl such as pyridyl, thienyl, imidazolyl or furanyl, optionally substituted with  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy,  $C_6-C_{10}$  aryloxy, heteroaryloxy,  $C_3-C_6$  alkenyloxy,  $C_3-C_6$  alkynyloxy, halogen; or  $S(O)_n$  -  $C_1-C_6$ alkyl  $C_1-C_6$  alkoxyaryl or  $C_1-C_6$  alkoxyheteroaryl;

A is -S-, -SO- or -SO<sub>2</sub>-;

$R^2$  and  $R^3$ , taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N- $R^7$  optionally having one or two double bonds;

R<sup>4</sup> is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R<sup>5</sup>;

C<sub>3</sub> to C<sub>8</sub> cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R<sup>5</sup>;

R<sup>5</sup> is H, C<sub>7</sub>-C<sub>11</sub> aroyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub> to C<sub>12</sub> alkyl, C<sub>2</sub> to C<sub>12</sub> alkenyl, C<sub>2</sub>-C<sub>12</sub> alkynyl, F, Cl, Br, I, CN, CHO, C<sub>1</sub>-C<sub>6</sub> alkoxy, aryloxy, heteroaryloxy, C<sub>3</sub>-C<sub>6</sub> alkenyloxy, C<sub>3</sub>-C<sub>6</sub> alkynyloxy, C<sub>1</sub>-C<sub>6</sub> alkylamino-C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>2</sub> alkylene dioxy, aryloxy-C<sub>1</sub>-C<sub>6</sub> alkyl amine, C<sub>1</sub>-C<sub>12</sub> perfluoro alkyl, S(O)<sub>n</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, S(O)<sub>n</sub>-aryl where n is 0, 1 or 2; OCOO C<sub>1</sub>-C<sub>6</sub> alkyl, OCOOaryl, OCONR<sup>6</sup>, COOH, COO C<sub>1</sub>-C<sub>6</sub> alkyl, COOaryl, CONR<sup>6</sup>R<sup>6</sup>, CONHOH, NR<sup>6</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>6</sup>R<sup>6</sup>, NR<sup>6</sup>SO<sub>2</sub>aryl, -NR<sup>6</sup>CONR<sup>6</sup>R<sup>6</sup>, NHSO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NHheteroaryl, SO<sub>2</sub>NHCOaryl, CONHSO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CONHSO<sub>2</sub>aryl, SO<sub>2</sub>NHCOaryl, CONHSO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub> alkyl, CONHSO<sub>2</sub>aryl, NH<sub>2</sub>, OH, aryl, heteroaryl, C<sub>3</sub> to C<sub>8</sub> cycloalkyl; saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR<sup>7</sup>, wherein C<sub>1</sub>-C<sub>6</sub> alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR<sup>7</sup> and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy;

R<sup>6</sup> is H, C<sub>1</sub> to C<sub>18</sub> alkyl optionally substituted with OH; C<sub>3</sub> to C<sub>6</sub> alkenyl, C<sub>3</sub> to C<sub>6</sub> alkynyl, C<sub>1</sub> to C<sub>6</sub> perfluoro alkyl, S(O)<sub>n</sub> alkyl or aryl where n is 0, 1 or 2; or COheteroaryl; wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR<sup>7</sup> and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy;

and R<sup>7</sup> is C<sub>7</sub>-C<sub>11</sub> aroyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>1</sub>-C<sub>12</sub> perfluoro alkyl, S(O)<sub>n</sub>-alkyl, S(O)<sub>n</sub>-aryl where n is 0, 1 or 2; COOalkyl, COOaryl, CONHR<sup>6</sup>, CONR<sup>6</sup>R<sup>6</sup>, CONHOH, SO<sub>2</sub>NR<sup>6</sup>R<sup>6</sup>, SO<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NHheteroaryl, SO<sub>2</sub>NHCOaryl, CONHSO<sub>2</sub>alkyl, CONHSO<sub>2</sub>aryl, aryl, or heteroaryl; where aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy; and heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or N-C<sub>1</sub>-C<sub>6</sub> alkyl; alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>; alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>; alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R<sup>5</sup>; arylalkyl of 7 to 16 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>; biphenylalkyl of 13 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>; arylalkenyl of 8 to 16 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>; cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, optionally substituted with one or two groups selected independently from R<sup>5</sup>; saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR-C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with one or two groups selected independently from R<sup>5</sup>; R<sup>8</sup>R<sup>9</sup>N-C<sub>1</sub>-C<sub>6</sub>-alkoxyaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl where R<sup>8</sup> and R<sup>9</sup> are independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl or R<sup>8</sup> and R<sup>9</sup> together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

The most preferred matrix metalloproteinase and TACE inhibiting compounds of this invention are:

1-benzyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

J=.029, 2H), 7.72-7.75 (d, J=.027, 2H), 7.87 (s, 1H), 9.37 (s, 1H), 10.53 (s, 1H), 11.18 (s, 1H).

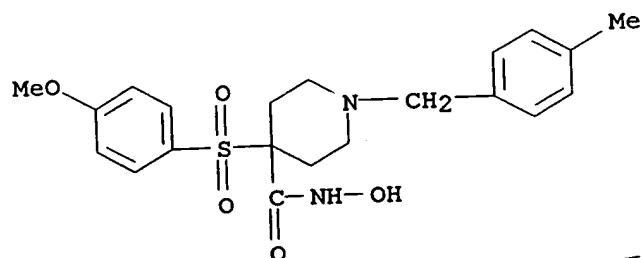
### Example 86

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#### 4-(4-methoxy-benzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid hydroxamide

Page 1

IN 4-Piperidinecarboxamide, N-hydroxy-4-[(4-methoxyphenyl)sulfonyl]-1-[(4-  
methylphenyl)methyl]- (9CI)  
MF C21 H26 N2 O5 S



Starting from 4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid was prepared  
starting from 4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester (4.3g,  
25 9.9 mmol) dissolve in methanol (30 mL), 10 N sodium hydroxide (10 mL),  
tetrahydrofuran (20 mL). The resulting reaction mixture was worked up as outlined in  
example 83. Yield 1.6 g (40 %). white solid mp 207-208 °C, MS: 404.3 (M+H)<sup>+</sup>.

Starting from 4-(4-methoxy-benzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid  
30 (1.59g, 3.9 mmol) and following the procedure as outlined in example 83, .505 g of 4-(4-  
methoxy-benzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid hydroxamide was  
isolated as a white solid. mp 176-177 °C; Yield 32%; MS: 419.0 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (300  
MHz, DMSO-d<sub>6</sub>): δ 2.24-2.32 (m, 2H), 2.51(t, 3H), 2.73-2.80 (m, 2H), 3.35-3.50 (m, 4H),  
3.87 (s, 3H), 4.24 (s, 2H), 7.13-7.17 (d, J=.039, 2H), 7.23-7.60 (d, J=.036, 2H), 7.38-  
35 7.41 (d, J=.025, 2H), 7.65-7.68 (d, J=.039, 2H).

cyclooctyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as a white powder. Yield 22%; mp >200 °C; MS: 425 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 1.42-1.66 (m, 14H), 1.83 (m, 2H), 2.33 (m, 2H), 2.67 (m, 2H), 3.30-3.51 (m, 3H) 3.88 (s, 3H) 7.17 (d, 2H), 7.66 (d, 2H).

5

### Example 95

#### 1-Ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide

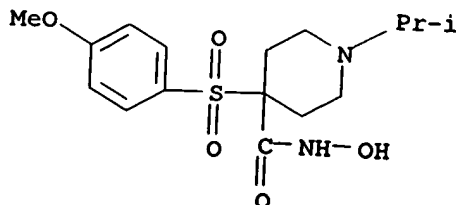
- 10 1-Ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example 83. Starting from 4-(methoxy-benzenesulfonyl) acetic acid ethyl ester (3 g, 11.6 mmol) and ethyl-bis-(2-chloro-ethyl)-amine (2.39g, 11.6 mmol). Yield 3.09 g, (75%); low melting brown solid; MS: 356 (M+H)<sup>+</sup>.
- 15 1-Ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid was prepared starting from 1-ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester (2.42 g, 6.8 mmol) dissolved in methanol (100 ml) and 10 N NaOH (15 ml). The resulting reaction mixture was worked up as outlined in example 83. Yield 1.29 g (58%); white solid; mp 209 °C; MS: 328 (M+H)<sup>+</sup>.
- 20 Starting from 1-ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid (1.23 g, 3.76 mmol) and following the procedure as outlined in example 83, 1.02 g of 1-ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off white powder. Yield 80%; mp 85 °C; MS: 343 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ
- 25 0.926 (t, J = 7.1 Hz, 3H), 1.68-1.89 (m, 4H), 2.05-2.24 (m, 4H), 2.73 (q, 2H), 3.85 (s, 3H), 7.07 (d, 2H), 7.64 (d, 2H).

### Example 96

#### 30 1-Isopropyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide

IN 4-Piperidinecarboxamide, N-hydroxy-4-[(4-methoxyphenyl)sulfonyl]-1-(1-methylethyl)- (9CI)

MF C16 H24 N2 O5 S



## Example 98

## 1-Benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide

5 1-Benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example 83. Starting from from 4-(butoxy-benzenesulfonyl) acetic acid ethyl ester (6 g, 20 mmol) and bis-(2-chloro-ethyl)-benzylamine (10 g, 30 mmol). Yield 5.15 g (56%); yellow oil; MS: 460 (M+H)<sup>+</sup>.

10 1-Benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid was prepared starting from 1-benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester (5.1 g, 11.1 mmol) dissolved in THF:methanol 3:1 and 10 N NaOH (10 ml). The resulting reaction mixture was worked up as outlined in example 83. Yield 2.66 g (56%); off white solid; mp 210 °C; MS: 432 (M+H)<sup>+</sup>.

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Starting from 1-benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid (2.61 g, 6.06 mmol) and following the procedure as outlined in example 83, 860 mg of 1-benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off white powder. Yield 32%; mp 144 °C; MS: 446.9 (M+H)<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>):

20 δ 0.94 (t, J = 7.3 Hz, 3H), 1.44 (q, J = 7.5 Hz, 2H), 1.70 (q, 2H), 2.28-2.32 (m, 2H), 2.50 (d, 2H), 2.74-2.83 (m, 2H), 3.35 (d, 2H), 4.08 (t, J = 6.3 Hz, 2H), 4.34 (s, 2H), 7.13 (d, J = 8.7, 2H), 7.45 (s, 3H), 7.54 (s, 2H), 7.74 (d, J = 8.7, 2H), 9.35 (s, 1H), 10.7 (s, 1H).

## Example 99

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## 1-(4-Fluoro-benzyl)-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid

hydroxyamide

IN 4-Piperidinecarboxamide, 1-[(4-fluorophenyl)methyl]-N-hydroxy-4-[(4-methoxyphenyl)sulfonyl]- (9CI)  
MF C20 H23 F N2 O5 S

